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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Nicholas S. BODOR)
Serial No.: 807,034) Group Art Unit: 125
Filed: December 9, 1985) Examiner: Lipovsky, J.
For : SOFT STEROIDS HAVING)
ANTI-INFLAMMATORY ACTIVITY)

DECLARATION

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

SIR :

I, Kazuyuki NAKAGAWA, of 774-1, Oomatsu, Kawauchi-cho, Tokushima-shi, Tokushima-ken, Japan, declare that

1) I graduated from Osaka University, Faculty of Pharmacy in March 1963. Since January 1964 up till the present, I have been in the employ of Otsuka Pharmaceutical Co., Ltd., assignee of the above-identified application, and have engaged in research works with respect to synthesis and development of various organic chemical and medical compounds in the research laboratory of this company. I had obtained a doctor degree in pharmacy from Osaka University in July 1981.

2) I am familiar with the subject matter disclosed in

the above-identified application as well as the disclosures in the references cited against the claims.

3) In order to demonstrate the difference between the inventions of the above-identified application and the cited references, the following experiments were conducted under my general direction and supervision.

Experiment 1

The compound of the invention was compared with the corresponding compounds taught by the cited references (i.e., Phillipps et al (1) and (2) and Sarret et al). These compounds were tested for the effects on granulation tissue formation and thymus weight caused by implantation of cotton pellet in rats in the same manner as described under the heading of GRANULOMA FORMATION TEST on page 38 of the Specification, and ED_{50}'s (for anti-granuloma effect), ED_{15}'s (for thymolysis) and therapeutic indices were determined from the test results obtained. The therapeutic indices were calculated according to the following equation:

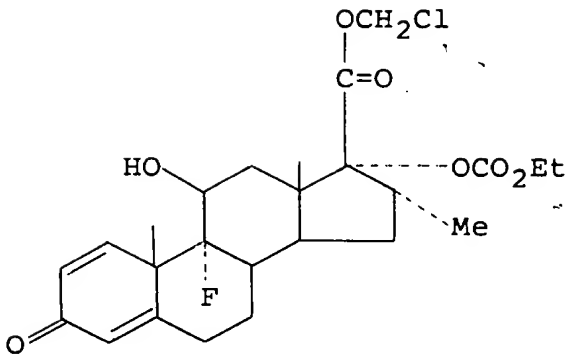
Therapeutic Index = T/A

where T is the ED_{15} value for thymolysis and A is the ED_{50} value for anti-granuloma. Thus, a significant increase in the therapeutic index is indicative of significant anti-inflammatory effect relative to lower side effect.

The compounds tested were as follows.

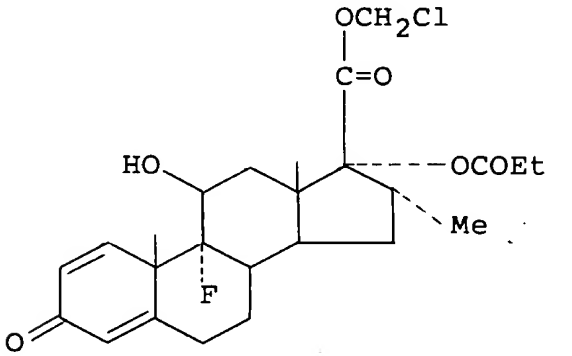
(A) The compound of Example 7A-3 of the present

invention:



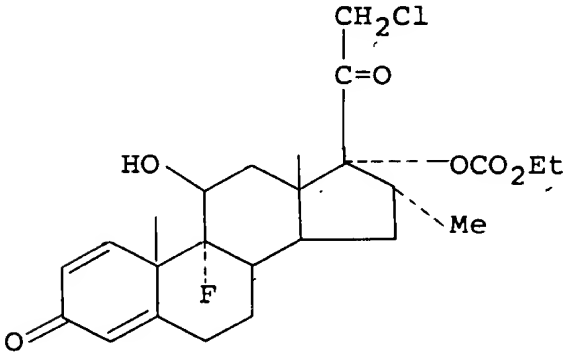
(A)

(B) The compound taught by Phillipps et al (1) and (2):



(B)

(C) The compound taught by Sarret et al:



(C)

The ED_{50}'s, ED_{15}'s and therapeutic indices of the above Compounds (A), (B) and (C) are shown in Table A below.

Table A

Test compound	Anti-granuloma ED_{50} (μg/pellet)	Thymolysis ED_{15} (μg/pellet)	Therapeutic Index
Compound (A)	1.07	33	30.8
Compound (B)	4.04	31	7.7
Compound (C)	6.3	27	4.3

Experiment 2

The compounds of the invention and a compound of Phillipps et al (1) and (2) were tested for the effect on granulation tissue formation caused by implantation of cotton pellet in rats in the same manner as described under the heading of GRANULOMA FORMATION TEST on page 38 of the Specification, and also tested for the effect on the thymus weight caused by the systemic (subcutaneous) administration thereof in the same manner as described under the heading of THYMUS INHIBITION TESTING on page 48 of the Specification. ED_{50}'s (for anti-granuloma effect), ED_{40}'s (for thymolysis) and therapeutic indices were determined from the results obtained. The therapeutic index was calculated according to the following equation.

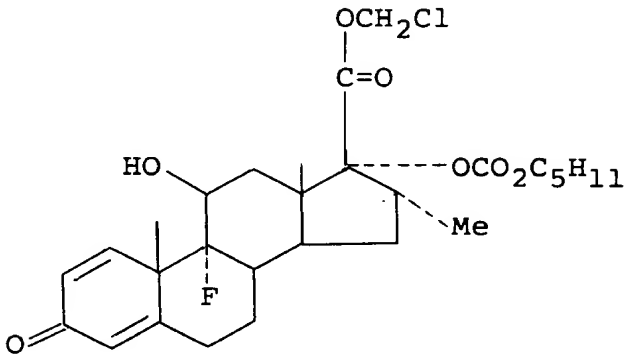
Therapeutic index = T/A

where T is the ED_{40} value for thymolysis and A is the ED_{50} value for anti-granuloma effect.

The compounds tested were as follows.

(1) The compounds of the present invention:

- Compound (A) as used in Experiment 1 (compound of Example 7A-3)
- Compound of Example 7A-23 which is represented by the fomula



(D)

This compound is referred to as "Compound (D)".

(2) The compound of Phillipps et al (1) and (2):

- Compound (B) as used in Experiment 1.

The results are shown in Table B below.

Table B

Test compound	Anti-granuloma ED_{50} (µg/pellet)	Thymolysis ED_{40} (mg/kg) s.c.	Therapeutic Index
Compound (A)	1.07	51.5	48.1
Compound (D)	3.05	>30	>9.8
Compound (B)	4.04	9.2	2.3

Consideration on the results of the experiments

As seen from Table A, the compounds of the invention having an ester group at 17β-position and carbonate ester group at 17α-position has unexpectedly higher therapeutic index, compared with the corresponding compound taught by Phillipps et al (1) and (2) having an ester group at 17β-position and acyloxy group at 17α-position, or compared with the corresponding compound taught by Sarret et al having an acyl group at 17β-position and carbonate ester group at 17α-position.

As seen from Table B, the compounds of the invention have high ED_{40} value for thymolysis also in the case of systemic (subcutaneous) administration, and thereby achieving higher therapeutic index than the compound of Phillipps et al.

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: July 6, 1987

Kazuyuki Nakagawa

Kazuyuki NAKAGAWA